HISTAMINE SHOCK. By H. H. DALE and P. P. LAIDLAW.

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In our earlier papers(1, 2, 3) on the action of histamine we have been chiefly concerned with the physiological analysis of the evanescent effects of smaller doses, though mention was made in our first paper of the phenomena of fatal histamine-poisoning in rabbits and guinea-pigs and of the prolonged collapse and coma caused by injecting large doses into the unanæsthetised cat. The essential difference between its actions in rodents and carnivora is well illustrated by the modifications introduced by anæsthesia. The normal rabbit or guinea-pig is easily killed by a relatively small intravenous injection of histamine, but suffers little harm from a much larger injection when deeply under the influence of an anæsthetic. We have shown that the cause of death in the guinea-pig is bronchial constriction, in the rabbit obstruction of the pulmonary circulation leading to acute dilatation of the right ventricle, and have pointed out that the reaction of plain muscle to histamine, on which the effects depend, is weakened by an anæsthetic. The unanæsthetised cat, on the other hand, recovers from the depressant effects even of very large doses, while in the same species under an anæsthetic even moderate injections of histamine often produce a fatal circulatory collapse and respiratory failure, from which the animal does not recover even after prolonged application of artificial respiration. E. Mellanby(4) has studied the onset of this condition in anæsthetised cats as the result of absorption of histamine from the small intestine. Our object in this paper is to examine the nature and the mode of production of this "histamine-shock" in anæsthetised cats. The fact that the condition has many features in common with a number of pathological conditions, loosely classified as "shock," gives to its analysis a more than immediate interest.

Methods. Most of our experiments have been made on cats, a few only on dogs. It will be clear from what has been said above that the

anæsthetic used has not merely the function of rendering the animal unconscious, but has some influence on the production of the effect we are studying. The precise nature of the adjuvant effect of the anæsthetic is not yet clear. It is not due to the presence of the anæsthetic as such, since a typical shock is produced by histamine in the decerebrated or spinal animal, after all traces of volatile anæsthetic have been removed. After recovery from a simple prolonged anæsthesia with ether, a cat remains for some time abnormally sensitive to the action of histamine, fatal shock being produced by a much smaller intravenous dose than that from which the normal unanæsthetised cat rapidly recovers.

Ether, following induction by chloroform, has been the anæsthetic in a large majority of the experiments. An animal under paraldehyde or urethane shows the effects quite typically, but in studying possibilities of resuscitation a volatile anæsthetic has the advantage that it can be lightened, discontinued and resumed in accordance with the need, as indicated by disappearance and revival of reflexes. The animals have, in most cases, been subjected to a minimum of operative preparation. A tracheal cannula was inserted to facilitate administration of the anæsthetic and to be ready for the application of artificial respiration at need. Cannulæ in one carotid artery and one femoral vein served for recording arterial pressure (mercury manometer) and making injections respectively. The other carotid artery was usually tied, clamped and cut to give samples of blood. Since failure of the vasomotor centre probably played some part in the later stages of the effect it was suspected that the restriction of its blood-supply by the ligature of both carotids might contribute to the result, when once the pressure had been reduced to a low level. The results were not perceptibly different, however, when one carotid was left patent and a femoral artery used for the collection of blood-samples. In a few experiments on the part played by the liver the circulation of this organ was short-circuited by a method which we have described in a recent note (5), the portal vein being connected to a renal vein or to the vena cava by means of an excised external jugular vein and Crile's anastomosis cannulæ. Throughout all experiments the animal was kept on an electrically heated table and an effort was made to eliminate any shock-producing factors other than those directly under examination.

The histamine used was the crystalline "Ergamine" phosphate of Burroughs Wellcome & Co. This is the diphosphate and contains roughly one-third of its weight of histamine base. Doses are expressed in milligrams of the base, the solution used being made up, as a rule, to contain

0·1 p.c. of this with 0·9 p.c. of sodium chloride. Solutions more than 24 hours old were not used; solutions of the phosphate, unless sterilised, rapidly lose their activity through the growth of bacteria in the solution.

Sudden injection of a large dose. When a dose of 1–2 mgm. of histamine per kilogram, dissolved in a few c.c., is rapidly injected into a vein, the action divides itself into three phases, two being brief preliminary effects, the third the main, lasting effect.

1. The immediate effect, usually beginning before the injection is completed, is a steep fall of the arterial pressure to the extent of 50 or 60 mm. This is undoubtedly due to lessened output from the left ventricle. Dale and Laidlaw(1) noticed this preliminary cardiac effect with an intermediate dose, showed that it was associated with shrinkage of a loop of bowel of which the volume was recorded, and attributed the effect to constriction of the pulmonary arterial branches. If the injection of a large dose is made into an animal with the chest opened, under artificial respiration, the distension of the right side of the heart during this initial fall of blood-pressure is very clearly apparent. In a record taken with Cushny's myocardiograph the contractions of the right ventricle are seen to become weakened and irregular during the period of overdistension. In one experiment death occurred at this stage from ventricular fibrillation. In an experiment on the heart-lung preparation from a dog Führer and Starling(6) observed a rise of pulmonary pressure on adding histamine to the circulating blood. This was accompanied by a rise of pressure in the left auricle, which, since the arterial resistance was artificial and constant, would seem to indicate a direct weakening of the action of the left ventricle. We are not in a position definitely to exclude such a direct weakening of the heart's action in the cat, though the fact that the isolated, perfused heart is stimulated by histamine to more rapid and ample contractions is against it. In any case we are convinced that this initial fall of arterial pressure is, in the main, the result of pulmonary arterial constriction. It is, therefore, an entirely different phenomenon from the rapid, purely vasodilator fall produced by a very small dose of histamine. It lasts only a few seconds; the distended right ventricle almost suddenly empties itself and resumes its normal, unembarrassed activity.

2. The second phase, beginning with the recovery of the heart from the first effect, sometimes appears merely as a brief arrest of the downward tendency of the arterial pressure, but frequently as a distinct secondary rise of pressure, which may even surpass the original level. If the vagi are intact this is obscured by a pronounced slowing of the

heart-beat, obviously due to action on the medullary centre, since it is abolished by section of the nerves. We usually eliminated this by cutting the vagi before the injection was given. This secondary phase of delay, partial recovery, or actual rise of arterial pressure, we regard as due to the arterio-constrictor effect, which histamine in large doses produces in virtue of its stimulant action on plain muscle. In the rabbit this is often its main effect on the circulation. In a cat in which a very low state of arterial tone has been produced, as by complete pithing, the immediate effect of injecting a large dose (1 mgm. or more) of histamine is to cause a rise of blood-pressure. A similar brief pressor effect follows

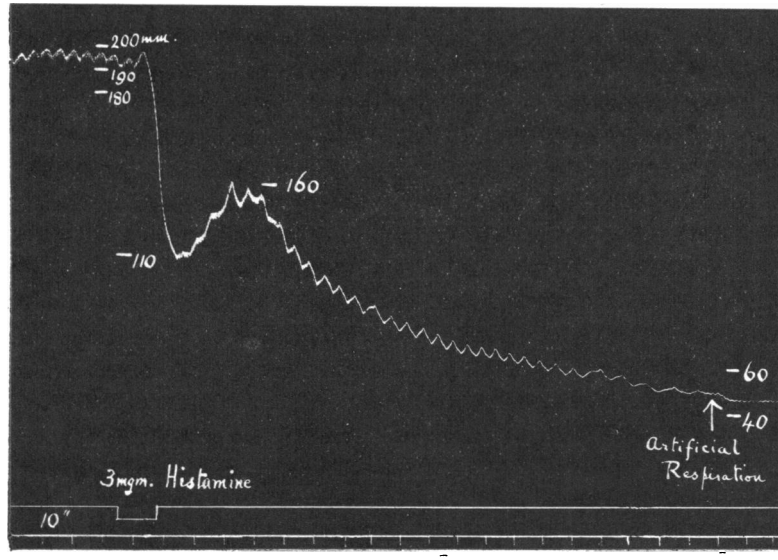

Fig. 1. Cat. 2·350 kilo.

injection of a second dose of histamine during the "shock" produced by the first dose. When it appears as the second phase of the effect of histamine, injected when the initial blood-pressure is high, this pressor effect only lasts from 10 to 30 seconds.

3. As the second phase of recovery or delay passes off the main fall of pressure begins. This is slow in comparison with the initial steep fall, and as it progresses the pulse-waves recorded by the manometer become rapidly smaller, until by the time the blood-pressure has reached its minimum (usually about 30–50 mm.), which is attained in about 4 to 10 minutes after the injection, the pulse is often hardly perceptible on

the tracing. Soon after the onset of the main fall of pressure the respiration becomes deep and laboured, then slower, and as a rule progressively weaker, till it ceases altogether and artificial respiration becomes necessary. Occasionally infrequent inspiratory gasps persist after the artificial respiration has begun. The application of artificial respiration does not arrest the fall of pressure; more often it seems to accelerate it. When the

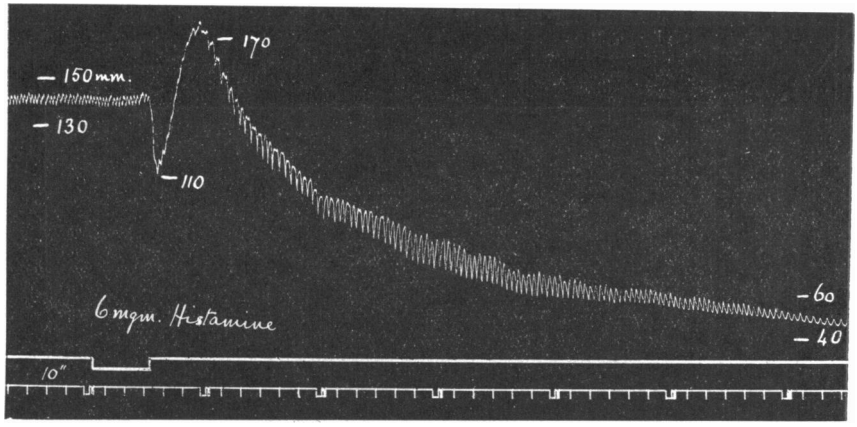

Fig. 2. Cat. 3·0 kilo.

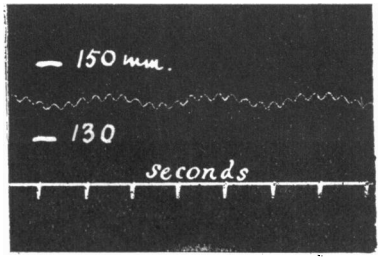

Fig. 3. Cat. 2·5 kilo. Normal.

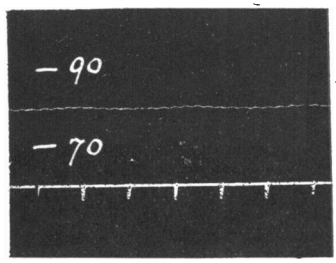

Fig. 4. The same, 10 minutes after injection of 5 mgm. of histamine.

effect has become fully developed the manometer float draws on the drum an almost level line, scarcely broken by the tiny undulations caused by the heart-beats and the artificial respiration. The different early phases of the effect on the blood-pressure are illustrated in Figs. 1–4. Fig. 1 shows in characteristic form the primary fall, secondary recovery, and third main fall of pressure, the heart-beats being no longer

perceptible on the record when the pressure has fallen to about 60 mm. Fig. 2 shows an example of less extreme effect, in which the respiration persists longer than usual. The secondary vaso-constrictor effect carries the pressure well above the original level in this instance. Figs. 3 and 4 show portions of another record, taken with a faster drum. Fig. 3 shows the arterial manometer record before, Fig. 4 the same 10 minutes after injection of 5 mgm. of histamine. It will be seen that the pulse transmitted to the manometer has already become extremely small when the pressure is still at about 80 mm. Figs. 5–7 illustrate the effect on a dog.

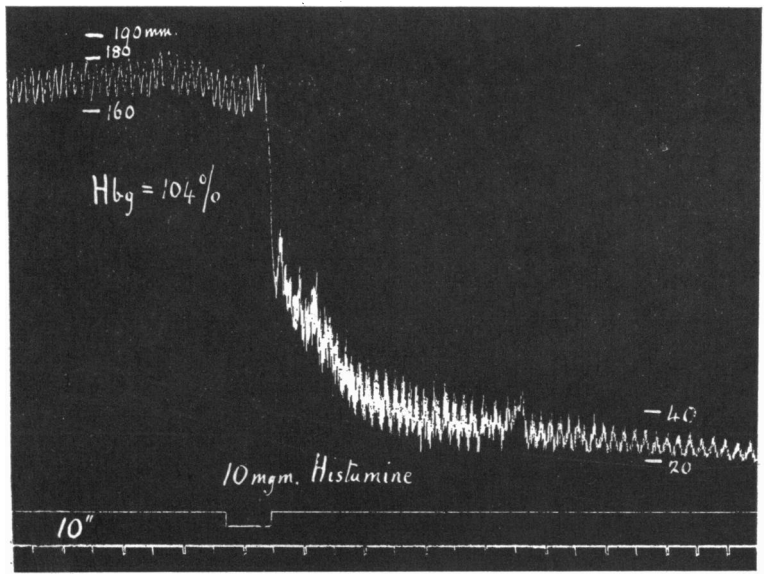

Fig. 5. Dog. 11 kilo.

The secondary rise of pressure is not seen in this animal, and the earlier stages of the fall are accompanied by pronounced dyspnœa. Otherwise the general features of the action are similar to those seen in the cat.

When the effect is fully developed the animal lies relaxed and apathetic, the corneal reflex is abolished, and the volatile anæsthetic can be discontinued. The mucous membranes show a blueish pallor. Unless the animal is artificially warmed the body temperature falls with great rapidity.

Slow infusion of histamine. The effect of a large dose of histamine suddenly injected, as described above, presents a curious contrast with

that of a small dose, as described in our earlier papers. The intense sudden vasodilator action of the small dose seemed to be so complicated by the concomitant vaso-constrictor action in the case of the larger dose, that the whole effect appeared, at first sight, to be of a different type. It was of interest to enquire, therefore, what would be the effect of the larger dose when slowly infused in more dilute solution, so that the whole injection occupied about 20 minutes instead of about 20 seconds. The solution was made up to contain 0·2 mgm. of histamine base per c.c. of physiological saline and, by means of a device for securing a slow, steady infusion, was run into the femoral vein at the rate of about 1 c.c. in 2 minutes, so that 0·1 mgm. entered the circulation in each minute, or 0·01 mgm. in 6 seconds. The onset of the infusion was followed by a

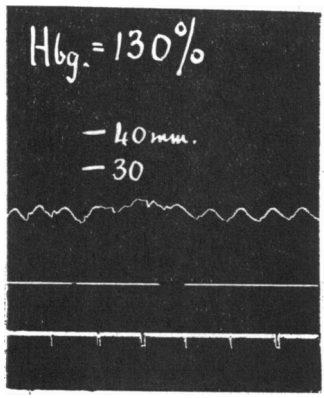

Fig. 6. Continuation of Fig. 5, 7 minutes after the injection.

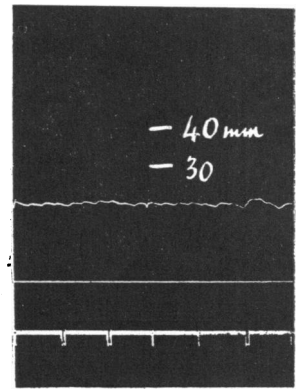

Fig. 7. The same 11 minutes after the injection.

prompt fall of blood-pressure from 160 mm. to 80 mm., such as would follow the injection of 0·01 mgm. The pressure, however, under the continued infusion, did not recover, but remained fairly steady at about 80–70 mm. until 0·6 mgm. in all had been injected. Then, with continued infusion, the output of the heart, as indicated by the pulse waves recorded by the manometer, began to decline and the pressure to fall further; meanwhile the respiration gradually became slower and weaker and then failed altogether. Artificial respiration was applied, but the pressure still declined and had fallen to 46 mm. by the time the injection of 1 mgm. was completed (13 minutes from the start). Thereafter the pressure slowly rose to 56 mm. with continued infusion. The natural respiratory movements were at this stage represented only by infrequent

convulsive inspirations, which appeared to be efforts at vomiting. By the time a total of 2 mgm. had been injected (representing a little more than 1 mgm. per kilo., the cat weighing 1·8 kilo.) the heart-beats were scarcely perceptible on the pressure tracing, while the pressure had returned to 46 mm. and continued to decline to 36 mm. after the injection had been completed. Portions of this record are reproduced in Fig. 8. It will be seen that the result of prolonging the time of injection, so that the amount of histamine circulating at any moment was probably always small, was to eliminate the first two phases of the effect of a sudden large injection, which we attributed to constriction of the pulmonary and systemic arteries, leaving only the shock-like third phase, with a more

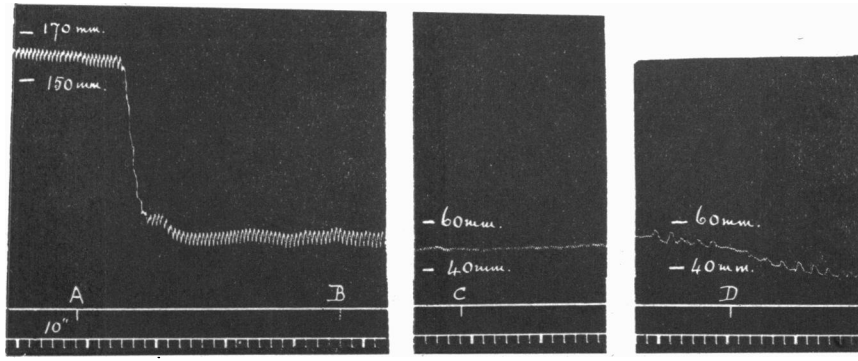

Fig. 8. Cat 1·8 kilo. At *A* begin infusion of 0·02 p.c. histamine. At *B* 1 c.c. in. At *C*, 13 minutes from the start, 5 c.c. = 1 mgm. in. At *D*, 25 minutes from the start, 10 c.c. = 2 mgm. in. Infusion stopped.

gradual and insidious onset. The connexion of this phase with the vasodilator effect of the single small dose is thus rendered obvious. When the vasodilator effect is perpetuated by continued slow infusion of the drug the shock-like failure of the circulation soon appears.

Analysis of the "Shock."

1. *The action on the heart.* A glance at the manometer record is sufficient to indicate diminution, almost to the point of extinction, of the output of the heart as a principal factor, if not the sole cause of the circulatory collapse. A casual inspection of such a record might easily suggest that we are dealing with a progressive primary failure of the heart's action. It soon becomes clear, however, that such an interpretation is incorrect. If the cardiac contractions had become so enfeebled

as the record at first sight suggests, we should expect the blood-pressure to have fallen to 20 mm. or less, whereas it often remains at 40, 50 or even as high as 70 mm. If the ear is applied to the chest wall the heart-sounds are well audible, even though the excursions of the mercury in the arterial manometer may be hardly sufficient to move the recording float. By lightly grasping the chest wall a relatively strong cardiac impulse can be detected. These auditory and tactile impressions of well-maintained muscular activity of the heart receive visual confirmation when the chest wall is opened. There is usually a slight excess of pericardial fluid, which somewhat obscures the movements of the heart until the pericardium is opened. This, however, is not the cause of the low blood-pressure and small pulse, since neither is improved by opening the

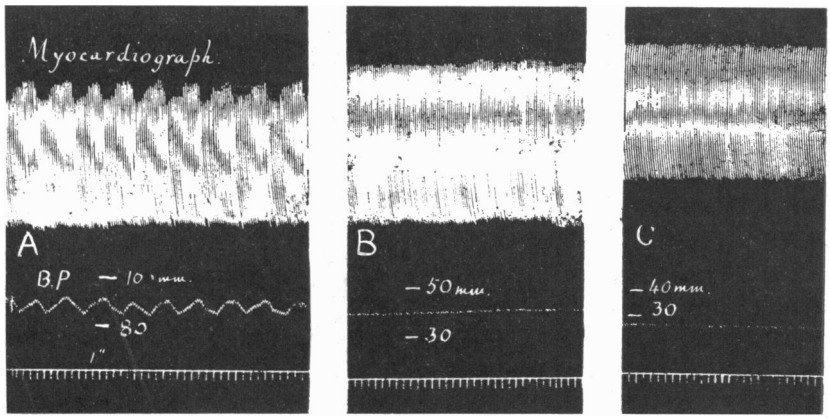

Fig. 9. Cat. 2·6 kilo. *A* normal, *B* 6 minutes, *C* 18 minutes after injection of 5 mgm. of histamine.

sac. When the heart is exposed it is seen to be beating with surprising vigour. The impression given by simple inspection is confirmed by a mechanical record of the contractions with the myocardiograph, as shown in Fig. 9. In this record the excursions of the lever recording the contractions of the right ventricle measure 25–29 mm. when the blood-pressure stands at about 90 mm., before the injection of histamine; 6 minutes after the injection, when the preliminary fall, due to cardiac embarrassment, and the secondary vaso-constrictor rise have given way to the main permanent fall of pressure, the lever excursions measure 32 mm., though the pressure has sunk to 44 mm., and still measure 26 mm. when the blood-pressure has reached 26 mm., 18 minutes after the injection.

Clearly the reduced output, so evident on the manometer record, is not due to weakening of the muscular contractions of the ventricles. When the circulation is failing from primary cardiac weakness the feebly beating heart is distended with blood, especially its right chambers. The heart of the cat in histamine shock is beating strongly, but the beats are ineffective because the heart is practically empty. The wall of the right ventricle is flaccid and folded in diastole; if the ventricles are squeezed between the fingers the effect on the arterial manometer is hardly perceptible; if a cut is made through the wall of either ventricle only a few drops of blood are expelled through the incision at each systole, and the outflow ceases altogether by the time some 10 c.c. have been ejected. The systolic output from the heart is failing because the diastolic filling is inadequate.

This failure of the heart to fill itself is, again, not due to defective diastolic relaxation. We are not able to exclude a slight increase in the tone, and consequent slightly diminished relaxation of the heart in diastole, as a possible direct effect of histamine on the heart muscle. Mere inspection of the beating heart easily gives the impression of increased tonus, since the eye cannot readily distinguish between defective relaxation of the muscle and inadequate filling from the veins. Several observers have stated that the tonus of the heart muscle is increased in surgical shock. It is quite clear, however, that imperfect relaxation is not to any significant degree responsible for the deficient filling of the heart in histamine shock, for the intrathoracic venæ cavæ are not distended, but flaccid and unusually empty. If 20 c.c. or so of warm saline solution are run into a jugular vein it can be seen that the chambers of the heart fill readily in diastole, and the filling is accompanied by a rapid recovery of the output and a rise of arterial pressure. The restorative effect of such a saline injection is but temporary, for reasons to be discussed later, and can be repeated many times. We may safely conclude that the failing output is due to some extracardiac condition affecting the venous return.

2. *The distribution of blood in the peripheral vessels.* We have already seen that the blood is not in the heart or in the venæ cavæ in the thorax. Plethysmographic records of the volume of organs give us little additional information in this case. A loop of bowel and a limb, after brief shrinkage during the initial fall and recovery of blood-pressure, both show a steady, slow increase of volume with the secondary, lasting decline of pressure. This, however, merely shows that the accumulation of blood at the periphery, which reasoning by process of exclusion shows to be occurring,

is not restricted to a particular area, but is taking place in abdominal viscera and skeletal muscles alike. Experience of the effect of other poisons having a generally similar type of action, as, for instance, of the effect of peptone in the dog, would suggest the probability of an accumulation of blood in the liver. Simple inspection of the exposed organ is sufficient to show that histamine does not produce this effect in the cat. The liver is not abnormally dark or swollen, and if incised it bleeds but little. The portal vein and its main tributaries are flat and collapsed, being even more conspicuously empty than the vena cava. If the lungs are allowed to collapse, by stopping the artificial respiration after the chest has been opened, it is obvious that they also are not to any significant degree congested with blood.

The blood, then, is not accumulated in the heart, or the great veins, which, on the contrary, are abnormally empty, or in the liver or the lungs, which are certainly not congested. Inspection further shows that the aorta, the main arteries, and even the finest arterial branches which can be distinguished on the surface of the intestine, contain very little blood. We have not investigated, by the method of comparative rates of perfusion, whether the arteries at this stage of the action are actively constricted. The fact that a further injection of histamine will produce a rise of pressure indicates that the initial vaso-constrictor effect has at least to some extent passed off. If there is still some constriction, this is not the reason for the small blood content, for the larger arteries are obviously flat and collapsed. The point of main interest for our purpose was that no part of the missing blood could be accounted for by accumulation on the arterial side of the circulation.

There remained the capillaries and venules, and here, at last, signs of accumulation of blood could be detected. The signs were clearest in the case of the abdominal viscera, possibly on account of the greater transparency of the tissues. If the abdomen was opened in the earlier stages of the main, secondary fall of the blood-pressure, the intestines looked diffusely and somewhat duskily red and the net-work of venules stood out distinctly. The pancreas had a purplish, congested appearance, which was seen in less degree in the lymphatic glands. At a later stage the general colour of the intestines was much bluer, while the pancreas became very obviously œdematous, the lobules appearing separated, as if embedded in a clear and colourless jelly. No other organ showed this pronounced œdema, nor was there any distinct accumulation of free fluid in the serous cavities, though the surface of the viscera was unusually moist. Several attempts were made to observe changes in the

calibre of capillaries under a moderate power of the microscope, without any result to which we could attribute importance. When the shock effect was well developed, the extreme slowness of circulation, amounting locally to practical stagnation of the blood, was observed in the microscopic venules. In the vessels where the flow was extremely sluggish the column of blood seemed often to be divided in segments, clear spaces, apparently only containing plasma, intervening between short columns of tightly packed corpuscles. There was no pronounced agglutination of the corpuscles, however, in blood removed from the carotid artery.

We have spoken of the great veins and their main tributaries as very empty and collapsed and of the capillaries and minute veins as full. The veins of intermediate size, such as the branches just leaving the wall of the bowel to join the veins in the mesentery, often showed a curious condition which deserves mention. They appeared to be irregularly constricted, so that a short stretch of vein, 2–5 mm. in length, distended to sausage-shape with blood, would intervene between sections in which the vein was reduced to a thread-like slenderness. It must be supposed that irregularly distributed tone of the plain muscle in the vein walls produced this condition. It should be noted, however, that it only appeared at a late stage of the action, when the circulation through the bowels was already extremely slow. It cannot, therefore, be regarded as pointing to constriction of the smaller veins as a factor in the production of the failure of the circulation.

We have examined the other organs of the body, and especially the skeletal muscles, as containing a large part of the whole capillary area, for signs of an accumulation of blood in the capillaries, similar to that which we detected in the walls of the bowel and in the pancreas. In the straightforward experiments we were unable to satisfy ourselves on this point, but in experiments where a state of plethora had been previously produced by transfusion of whole blood from another cat the general peripheral engorgement produced by histamine was very striking. In two experiments of this type anastomosis was made between the jugular veins of two cats under ether by means of Crile's cannula, and it was arranged that the larger animal in each case should serve as the donor to the smaller, which was the experimental animal. Transfusion before the administration of histamine did not materially alter the response in the experimental animal. In one experiment profound shock resulted and a further transfusion did not bring about any permanent improvement. *Post mortem* the congestion of the visceral capillaries was very remarkable and the exsanguinated cat alongside made a very vivid contrast.

The colour and general appearance of the intestines resembled that met with in early strangulation of the bowel, yet the veins were not distended. The liver was of a dark plum-colour, but not obviously enlarged, and the skeletal muscles were deep red and obviously contained much blood. Unfortunately the corpuscular content of the blood was not determined before administering histamine, but it cannot be doubted that a pronounced concentration occurred, since the subsequent hæmoglobin reading was 140 p.c. and the count of the red cells 13,250,000 per cmm. This evidence that part of the missing blood collects in the capillaries of the voluntary muscles is confirmed by the observation, to be described later, that the condition of shock can be produced by histamine after removal of the abdominal viscera. Mention may here be made of an attempt to measure the distribution of blood between the abdominal viscera and the rest of the body.

A cat was anæsthetised with ether, and a sample of blood taken from a carotid artery. The abdomen was then opened in the middle line, the rectum was double ligatured and cut through as low down as possible, and the œsophagus treated similarly just below the diaphragm. Double ligatures were then laid round (1) the inferior mesenteric artery, (2) the superior mesenteric artery and the cœliac axis close to their origin from the aorta, (3) the portal vein above the points of entry of the splenic and pancreaticoduodenal veins, and (4) the vena cava just below the liver. A single ligature was passed round the vena cava between the liver and the diaphragm. When all was ready one of the ligatures on each of the arteries to the intestine and stomach and on the portal vein was drawn tight, the cooperation of three persons, working to a signal, ensuring simultaneous occlusion of all. Without delay the ligatures on the vena cava above and below the liver were then tied, the chest was immediately opened, the heart was ligatured, and the inferior vena cava tied above the diaphragm. We now had the animal dead, but had shut into (1) the vessels of the stomach, intestine and spleen, (2) those of the liver, and (3) the rest of the body, the amounts of blood which they respectively contained during life, under the conditions of circulation existing at the moment when the ligatures were tied. Not much stress could be laid on the blood content of the liver, since the portal vein was tied some seconds before the vena cava. Our main object however—a determination of the fractions of the total blood in the intestines and in the rest of the body—could now be attained. The arteries were ligatured again and cut between the ligatures. The portal vein also was again ligatured close to the portal fissure and cut through. The stomach, intestines and spleen could now be removed entire, without loss of blood, to a large dish. Cannulæ were inserted into the arteries and infusion was carried out through each in turn with oxalated saline solution, the portal vein being slit open to allow free outflow. The washing was continued till no blood could be detected in any vessels and the outflowing fluid was colourless. The mixed washings were carefully collected and made up to an exact volume. The liver was next removed, with the closed section of the vena cava attached to it, and was similarly washed out completely through the portal vein; periodical occlusion of the outflow through the vena cava, causing temporary distension of the liver, greatly assisted the complete exsanguination. Finally the blood in the rest of the body was washed out, infusion being made into the root of the aorta, with outflow cannulæ in the abdominal vena cava and the right auricle, and into the pulmonary artery, with an outflow cannula in the left auricle.

The blood from the ventricles was washed out and added. We had thus three measured quantities of saline containing the blood (1) in the stomach, intestines and spleen, (2) in the liver, and (3) in the rest of the body, arrested at a moment of normal circulation. The corpuscles in each were completely hæmolysed by adding ether and shaking, and the solutions were then freed from suspended traces of cellular debris by centrifuging. The volume of blood in each was then estimated by colorimetric determination as CO-hæmoglobin against an accurate dilution of the original blood. A precisely similar determination was then carried out on another cat, in which the ligatures on the vessels were tied at the height of the shock produced by histamine. The results were as follows:

1. Normal cat. Weight 2·3 kilo. Calculated blood volume (taken as 48 c.c. per kilo.) = 110 c.c.

The following dilutions gave equal depths of colour.

Normal carotid blood × 82.
Washings from liver (800 c.c.) × $\frac{58}{50}$.
Washings from stomach, intestine and spleen (500 c.c.) × $\frac{96}{50}$.
Washings from remainder (2000 c.c.) × $\frac{156}{50}$.

Liver blood	$=\frac{800 \times 58}{50 \times 82}$ c.c.	= 11·3 c.c.	= 10·3 p.c.
Stomach, intestine and spleen blood	$=\frac{500 \times 96}{50 \times 82}$ c.c.	= 11·7 c.c.	= 10·6
Blood from remainder	$=\frac{2000 \times 156}{50 \times 82}$ c.c.	= 76·1 c.c.	= 69·2
Total recovered		= 99·1 c.c.	= 90·1

2. Cat under histamine shock. Weight 2·35 kilo. Calculated original blood volume = 113 c.c.

The following dilutions gave equal depth of colour:

Carotid blood (before histamine) × 72.
Liver washings (700 c.c.) × $\frac{62}{50}$.
Washings from stomach, intestine and spleen (500 c.c.) × $\frac{82}{50}$.
Washings from remainder (2500 c.c.) × $\frac{93}{50}$.

Liver blood	= 12·0 c.c.	= 10·6 p.c.
Stomach, intestine and spleen blood	= 11·4 c.c.	= 10·1
Blood from remainder	= 64·6 c.c.	= 57·2
Total recovered	= 88·0 c.c.	= 77·9

It is difficult to draw from these figures a definite conclusion as to a change in distribution of the blood, as between the abdominal viscera and the rest of the body, in histamine shock. Of the blood removable by washing out the vessels with saline, that from the abdominal viscera bore a higher proportion to that from the rest of the body in the case of histamine shock than in the normal control. On the other hand the blood from the abdominal viscera in histamine shock does not form an abnormally large fraction of the original total volume of blood in the body, as calculated from the body weight. Its apparent increase in proportion to the blood from the rest of the body is due to reduction of the

latter; the total amount obtainable by washing being only about 78 p.c. of the calculated volume, as compared with 90 p.c. in the normal animal. This suggests that there are probably capillary areas in which the corpuscles have become adherent, or condensed into solid columns, so that washing does not remove them.

An experiment of a somewhat different kind was made to determine the distribution of blood between large vessels, on the one hand, and small vessels and capillaries on the other.

In a cat under ether the abdomen was opened, the small intestine was cut through at two points, and the separated loop washed out thoroughly and tied at each end. The mesentery was then slit down to the root opposite each cut. Two ligatures were laid round the vessels of this isolated triangular segment of mesentery as near to the root as possible. The mesentery with the attached segment of intestine was then carefully spread out on a glass plate covered with thin rubber membrane. The preparation was carefully kept warm and moist by swabs of warm saline. At a given moment one observer tied the vessels of the segment of mesentery near the root, while the other occluded them close to the intestinal wall by pressure between the edge of a circular glass Petri-dish of suitable size and the rubber-covered plate. The second ligature near the root of the mesentery was then tied, and by cutting between the ligatures the preparation was freed and could be lifted from the body while the peripheral occlusion was maintained. With a sharp knife the loop of intestine was then separated by a cut peripheral to the compression and dropped immediately into a vessel containing oxalated saline solution. The pressure was then released and the wedge of mesentery with its vessels, together with blood which exuded from them on to the plate, was washed into a separate similar vessel. The loop of intestine was slit open and thoroughly squeezed and kneaded in the saline till it looked quite white. It was then removed, minced and ground with sand and washed with further saline, but as these washings were practically colourless they were discarded. The mesenteric vessels were squeezed thoroughly free from blood in the other dish. The two sets of washings were then made up to exact volumes, hæmolysed with ether, centrifuged and compared colorimetrically with a dilution of blood from the carotid artery in distilled water.

Arrangements being made to record blood-pressure and give intravenous injections, the cat now received 5 mgm. of histamine intravenously. (The body weight being 2·8 kilo. this amounted to about 1·8 mgm. per kilogram.) When the shock had completely developed, an adjoining, shorter loop of small intestine was treated in exactly the same way as the first. It will be shown later that the proportion of corpuscles to plasma is greatly increased in histamine shock. The determinations, however, were all made with reference to dilutions of the original blood.

The following were the figures obtained:

1. Before histamine.

Washings from intestinal wall—26 c.c. diluted $\frac{81}{50}$ matched carotid blood diluted 128-fold

$$\frac{26 \times 81}{50 \times 128} = 0{\cdot}33 \text{ c.c.}$$

Washings from mesenteric vessels—22 c.c. diluted $\frac{115}{50}$ matched carotid blood diluted 64-fold

$$\frac{22 \times 115}{50 \times 64} = 0{\cdot}79 \text{ c.c.}$$

2. During histamine shock.

Washings from intestinal wall—43 c.c. diluted $\frac{65}{50}$ matched carotid blood diluted 128-fold

$$\frac{43 \times 65}{50 \times 128} = 0{\cdot}44 \text{ c.c.}$$

Washings from mesenteric vessels—33 c.c. diluted $\frac{64}{50}$ matched carotid blood diluted 128-fold

$$\frac{33 \times 64}{50 \times 128} = 0{\cdot}33 \text{ c.c.}$$

The ratios $\frac{\text{blood in large vessels}}{\text{blood in small branches and capillaries}}$ are, therefore, in the two cases:

$$\text{normal} \quad \ldots \quad -\frac{0{\cdot}79}{0{\cdot}33} = 2{\cdot}4,$$

$$\text{histamine shock} \quad -\frac{0{\cdot}33}{0{\cdot}44} = 0{\cdot}75.$$

These measurements confirm the visual impression that an essential factor in the failure of circulation, which we have called "histamine shock," is an accumulation of the blood in the minute vessels at the periphery, so that the larger vessels, both arteries and veins, are depleted, and the output from the heart falls to a very low level, owing to a gross deficiency in the venous inflow. The measurements do not indicate that this peripheral accumulation is restricted to any particular part of the system; the evidence points rather to its occurrence in all organs of the body alike. We shall see later that this is confirmed in another way.

3. *Changes in the blood.* (*a*) *Estimates of corpuscular content.* If a small sample of blood be taken from the carotid artery before the injection of histamine, and another when the "shock" has become thoroughly developed, a striking increase in the corpuscular content is usually found. This can be detected either by the hæmatocrit, by the hæmoglobinometer, or by counting the cells with a hæmocytometer. Having satisfied ourselves that these different methods gave parallel results, we adopted the hæmoglobinometer (Gowers-Haldane) for routine use, sometimes checking the results by use of the hæmatocrit. The samples were taken into small tubes containing a pinch of dry, finely powdered potassium oxalate, and all determinations of corpuscular content made at the end of the experiment.

The following record from an actual experiment illustrates the procedure and the type of result observed:

Cat weighing 2·35 kilo., anæsthetised with chloroform followed by pure ether. Right carotid dissected for taking blood samples; cannula in left carotid for recording arterial pressure. Injections into femoral vein.

3.26 p.m.—arterial pressure	175 mm.	Blood sample No. 1.
3.32 p.m. „ „	173 mm.	Inject 5 mgm. of histamine.
3.38 p.m. „ „	40 mm.	Blood sample No. 2.
3.42 p.m. Animal killed for examination of tissues.		

	Hæmoglobinometer	Hæmatocrit
Sample No. 1	72 %	30 %
„ 2	120	50

It will be noticed that the proportion between the two readings is the same by either method, being 3 : 5.

In other experiments, in which a similar comparison was made, the following values were obtained:

TABLE I.

	Hæmoglobinometer			Hæmatocrit		
	Normal	Shock	Ratio	Normal	Shock	Ratio
1.	78	116	1·49	33	50	1·5
2.	80	120	1·5	33	50	1·5
3.	92	130	1·4	33	50	1·5
4.	80	118	1·3	40	52	1·3

It will be seen that, within the limits of accuracy of the methods, the proportions between the readings before and after histamine correspond. It will be seen, also, that the normal corpuscular content of the cat's blood does not often vary very much from about 33 p.c. by volume, while the hæmoglobin value varies more widely. Without any serious error, therefore, we can deduce hæmatocrit readings from hæmoglobinometer readings, in cases where only the latter were made, by assuming that the initial, normal hæmoglobin-reading corresponded to a corpuscle-content of 33 p.c., and that the change in relative corpuscular volume was proportional to the change in hæmoglobin value. The following table shows the arterial pressure and the hæmoglobin readings from arterial blood before the injection of histamine and at the height of the histamine shock in a number of cats, including those quoted above.

TABLE II.

Blood-pressure in mm. of mercury		Hæmoglobin %	
Normal	Histamine shock	Normal	Histamine shock
175	40	72	120
173	40	92	130
143	70	80	98
206	46	96	142
188	64	96	148
150	34	70	100
160	62	70	110
218	76	82	106
188	77	82	108
139	40	70	122
190	50	80	106
140	45	78	115
150	60	64	96

In all these cases the increase in hæmoglobin value is pronounced, though its extent is somewhat variable.

A single example will suffice to demonstrate the parallelism between the change in hæmoglobin value, corpuscular volume by hæmatocrit, and red-cell count.

Hæmoglobinometer			Hæmatocrit			Red cells per c. mm.		
Normal	Shock	Ratio	Normal	Shock	Ratio	Normal	Shock	Ratio
74	98	1·32	30	40	1·33	8,344,000	11,360,000	1·36

When we consider the methods by which a rapid change of this nature could be produced, only two possibilities present themselves—loss of fluid from the blood vessels, or the washing into circulation of accumulations of corpuscles from some depot where they normally lie stationary. The close correspondence between the hæmoglobin and hæmatocrit readings is, on the whole, not in favour of the latter explanation; it might be expected, perhaps, that corpuscles thus freshly added to the circulation would have a perceptibly different hæmoglobin index from that of those normally circulating. The argument is not a very strong one, however, and must have less weight than the difficulty due to the consideration, that the production of the change in this way would necessitate the presence in the body, but not in circulation, of at least half as many corpuscles as are normally circulating.

There is no such difficulty in supposing that the increase in the proportion of corpuscles is due to passage of fluid from the blood into the tissues. Evidence of such passage is to be found in the accelerated flow of lymph from the thoracic duct, under the influence of histamine, as described in an earlier paper (Dale and Laidlaw(2)).

(*b*) *Direct measurement of plasma volume.* This supposition, that the increase in corpuscular content was wholly due to loss of fluid from the blood, was directly confirmed by the use of "vital red," introduced by Keith, Rowntree and Geraghty(7). "Vital red" is the name given by these authors to a complex dye, which they found to be physiologically very inert, to have practically no tendency to stain the tissues, and to be excreted very slowly. If a small dose of this substance, in watery solution, is injected into the circulation, its dilution in the plasma can be colorimetrically estimated in a sample taken a few minutes later. An equal amount of the normal plasma is added to the standard dilution of the dye which is used for comparison. After an interval a further injection of the dye can be given and the measurement repeated, a sample of plasma taken just before this second injection being, in this case, added

to the control dilution. One such experiment may be described in detail, as it illustrates well the concordance of the results obtained by the different methods.

Cat weighing 2·3 kilo. Anæsthetised with chloroform, followed by ether. Arterial pressure from the left, samples of blood from the right carotid artery. Vagi cut.

3.25 p.m. Blood-pressure 170 mm. Bled 5 c.c. for control plasma (S 1).
3.29 ,, B.P. 156 mm. Inject 0·8 c.c. of 1 p.c. vital red into femoral vein.
3.33 ,, B.P. 136 mm. Bled 5 c.c. for colorimetric estimation (S 2). B.P. sinks to 110 mm. Lighten ether.
3.54 ,, B.P. steady at 124 mm.
3.56 ,, Inject 3 mgm. of histamine into femoral vein. B.P. falls rapidly to 96, rises again to 120, and then falls steadily, with slowing of respiration.
3.59 ,, B.P. 55 mm. Respiration fails. Artificial respiration applied. Corneal reflex absent. Ether discontinued.
4.0 ,, B.P. 40 mm.
4.0 to 4.3 p.m. Bled 4 c.c. (very slow flow from carotid) for second control plasma (S 3).
4.4 ,, B.P. 34 mm. Inject 0·8 c.c. vital red into femoral vein.
4.6 ,, Infrequent, inefficient inspiratory spasms. Artificial respiration continued.
4.8 ,, B.P. 37 mm. Bled 5 c.c. for second colorimetric estimation (S 4). B.P. sinks to 26 mm.
4.10 ,, Abdomen and thorax opened. Bowels show general purplish flush. Venules distinct, with very dark blood. Portal vein collapsed, with very little blood. Vena cava inferior not well filled. Heart beating vigorously, but chambers almost empty. Pancreas dusky in colour and very œdematous. Cat killed.

Estimations on blood.
Colorimetric.

1. *Normal*—Standard dilution—1 part plasma S 1, 2 parts vital red, 1 p.c. $\times \frac{1}{200}$, 1 part saline.
Test solution—1 part plasma S 2, 3 parts saline.
Reading with Dubosq colorimeter—Standard 10, Test 10·9.
Then if V_1 = the volume of plasma in the cat,

$$\frac{0{\cdot}8}{V_1} \times \frac{1}{4} \times 10{\cdot}9 = \frac{1}{200} \times \frac{1}{2} \times 10.$$

$$\therefore\ V_1 = 0{\cdot}8 \times 109 = 87{\cdot}2 \text{ c.c.}$$

2. *During histamine shock.*
Standard dilution—3 parts plasma S 3, 8 parts vital red, 1 p.c. $\times \frac{1}{200}$, 1 part saline.
Test solution— 1 part plasma S 4, 3 parts saline.
Reading with colorimeter—Standard 10, Test 8·5.
Then if V_2 = the volume of the plasma during shock,

$$\frac{0{\cdot}8}{V_2} \times \frac{1}{4} \times 8{\cdot}5 = \frac{1}{200} \times \frac{8}{12} \times 10.$$

$$\therefore\ V_2 = 6 \times 8{\cdot}5 = 51{\cdot}0 \text{ c.c.}$$

Hæmatocrit	Normal	15·5 in 38·5 = 40 p.c. corpuscles, 60 p.c. plasma.
	Shock	21 in 40·5 = 52 p.c. corpuscles, 48 p.c. plasma.
Blood volumes	Normal	$87{\cdot}2 \times \frac{100}{60} = 145{\cdot}3$ c.c.; Shock $51 \times \frac{100}{48} = 106$ c.c.
Hæmoglobinometer	Normal	90.
	Shock	118.

From V_1 and the normal hæmatocrit reading we can calculate the original volume of corpuscles, $87{\cdot}2 \times \frac{4}{6} = 58{\cdot}1$ c.c. This has been reduced, however, before the second estimation by two bleedings of 5 and 4 c.c. respectively, of which the first contained $\frac{4}{10} \times 5 = 2$ c.c., and the second $\frac{52}{100} \times 4 = 2{\cdot}1$ c.c.; total = 4·1 c.c. of corpuscles. The corpuscle-volume at the time of the second injection of vital red may be taken as $58{\cdot}1 - 4{\cdot}1 = 54$ c.c. (The direct determination above gives $106 - 51 = 55$ c.c.) From this the second plasma volume should be $54 \times \frac{48}{52} = 49{\cdot}8$ c.c., which corresponds as closely as can be expected with the 51 c.c. determined by vital red. We shall see later that under different conditions the loss of volume determined by vital red may be far greater than that indicated by the change in corpuscular content. The hæmoglobinometer readings as usual correspond closely with those by hæmatocrit; $90 \times \frac{52}{40} = 117$, as compared with 118 found.

It will be noted that the blood volume determined by vital red is considerably in excess of the 48 c.c. per kilo. based by some observers on exsanguination experiments. In the above case it is about 63 c.c. per kilo.

(*c*) *Nature and degree of the loss of fluid.* The change in the relative volumes of plasma and corpuscles being thus proved to be wholly due to diminution of the volume of the plasma, it was necessary to enquire what constituents of the plasma were involved in the change. It might be due to abstraction only of water and diffusible constituents, or to actual loss of plasma. The point has an important bearing on the nature of the action. Estimates were therefore made of the composition of the plasma before and during the shock. The proteins being the constituents concerning which information was required, determination of the refractive index was considered a sufficient indication. In one experiment part of each blood sample was oxalated with a constant proportion of solid potassium oxalate and plasma obtained; part was allowed to clot and the serum separated for estimation. In another experiment all samples were taken without oxalate and measurements made on serum only. In neither case was any important change detected in the protein content. The results of the second experiment may be quoted.

Cat weighing 3·8 *kilo.*

	Arterial blood-pressure	Hæmoglobinometer	Protein percentage in serum by refractometer
3.43 p.m.	240 mm.	88	8
3.45 „	4 mgm. histamine		
3.46 „	140	94	7·7
3.47 „	86	114	7·3
3.50 „	78	130	7·0
3.52 „	90	124	7·0
3.57 „	92	121	7·1
4.11 „	154	108	7·0
4.19 „	144	104	7·0

It will be seen that the shock-effect in this case was of a relatively weak and very rapidly evanescent nature, but the corpuscular content of the blood nevertheless showed a remarkable increase. At the same time the serum showed no increase of its protein. There was, indeed, a small decrease, the occurrence of which can only be explained by supposing that loss of plasma from one part of the circulation was accompanied by some absorption of water in another part. A similar reduction in the volume of the plasma, accompanied by lessening of the proportion of its solid constituents, has been recorded in traumatic shock. The main point, however, is the absence of any concentration of the plasma. The hæmoglobin values indicate a loss of nearly one-half of the plasma volume, so that if the diminution were due to abstraction of diffusible constituents only, the protein content should be nearly doubled instead of slightly diminished.

In the case quoted, in which the volume of the plasma was directly determined by vital red, it diminished from 87 c.c. to 51 c.c.—a loss of 41 p.c. In other instances an even greater proportionate loss can be calculated from the hæmoglobin or hæmatocrit figures. Thus, in the experiment detailed above, the hæmoglobin value rose from 88 to 130. If we assume a normal corpuscular volume of 33 p.c., this rises to $33 \times \frac{130}{88} = 49$ p.c. Representing the constant volume of corpuscles as 1, the volume of plasma declines from 2 to $\frac{51}{49}$—a loss of practically one-half of the original volume. In another instance the hæmoglobin value rose from 70 to 122, and the corpuscular volume from (say) 33 p.c. to 57 p.c. Again taking the volume of corpuscles as 1, we have the plasma volume declining from 2 to 0·75, *i.e.* a loss of 60 p.c. of the plasma originally present.

(*d*) *Location of the effect.* In earlier papers we have shown that the evanescent vasodilator effect of small doses of histamine is not limited to any particular organ or tissue. It seemed possible, however, that the loss of plasma from the blood would have a less general distribution. From analogy with the action of peptone, the effect of which in producing accelerated flow of lymph in the dog was shown by Starling to be due mainly to action on the liver, it seemed possible that the lymphagogic effect of histamine in the cat would show a similar restriction. We, therefore, in a series of experiments, diverted the blood from the liver by the method which we have recently described (5). When the action of histamine was tested with the liver thus excluded we observed, in one experiment, a fall of blood-pressure of relatively small extent, with practically no change in the proportion of corpuscles, and rapid

recovery of the blood-pressure to little below its original level. In subsequent experiments of the same kind, however, we observed the typical, lasting shock-effect after histamine, with pronounced increase in the proportion of corpuscles. We had a similar experience in testing the effect on the action of histamine of removing the whole of the abdominal portion of the alimentary canal and tying off the liver. In one case the eviscerated animal showed a relatively small and evanescent fall of blood-pressure, with a small loss of plasma from circulation, as the result of a large dose of histamine; in other similar experiments, however, a typical shock was produced, with an increase of the corpuscular content of the blood not less than that seen in some of the cases quoted above, in which the abdominal viscera were in normal connexion with the circulation. The following are details from two such experiments, in which about 1 mgm. of histamine base per kilogram was injected after removal of the stomach, intestines and spleen and exclusion of the liver from circulation.

Arterial pressure		Hæmoglobin per cent.	
Before	After injection of histamine	Before	After
173 mm.	40 mm.	92	130
143	70	80	96

We have met with cases of unusual resistance to the effect of histamine also in cats with the abdominal viscera in normal connexion with the circulation; indeed, at one period we encountered several such cases in successive experiments, in which even several milligrams of histamine per kilogram caused only a temporary fall of pressure, without extreme reduction of cardiac output, and with only slight increase in the proportion of corpuscles. We do not know the reason of this variability of the reaction, but its occurrence under normal conditions deprives of significance the occasional failure of the "shock" in the eviscerated animal. The fact that a typical effect is often seen after removal of the bowels shows that the blood vessels in general are liable to the action, and those of the abdominal viscera not conspicuously more so than others.

(*e*) *Effect on the other cellular elements in the blood.* We found that the proportion of leucocytes in the arterial blood underwent a conspicuous diminution during histamine shock, even when that of the red corpuscles was greatly increased; that is to say the effect of the loss of plasma was more than compensated by loss of leucocytes. The diminution was due largely to loss of polymorphonuclear cells, the eosinophiles being reduced to a smaller extent, and the lymphocytes hardly at all. In other words

the different types of cells were affected in the order of their amœboid activity. The magnitude of the change in the leucocytic count had no relation to the extent of the loss of plasma; it was at least as conspicuous when the shock was produced by slow infusion, with but little concentration of red corpuscles, as when great concentration occurred as the result of a single large injection of histamine. We do not regard the phenomenon as having any specific significance, since we have observed a leucopenia of the same type as the result of a prolonged fall of blood-pressure produced in other ways—*e.g.* by complete pithing or by slow infusion of acetyl-choline. Presumably any condition of low arterial pressure, with resultant slowing of the blood-flow, causes a tendency for the more amœboid corpuscles to adhere to the endothelium of the vessels and to pass, for the time being, out of the current of circulating blood. It may be recalled that a similar leucopenia was described by Biedl and Kraus(8) in anaphylactic shock in the dog, and has long been familiar in the very similar condition produced in the same animal by peptone. It was stated, however, that in these cases the polymorphonuclear leucocytes accumulated especially in the capillaries of the liver, the organ principally affected by poisoning of these types in the dog.

Another phenomenon, the significance of which is difficult to appraise, deserves mention, since we have repeatedly observed it in blood from animals in histamine shock. If a film is made from such blood and stained in the ordinary way, it is seen to contain numerous large clumps of agglutinated platelets. We received a decided impression that the platelets were not merely agglutinated but abnormally abundant, even in proportion to the increased content of red corpuscles, but we have no quantitative data. In 1914 v. Behring(9) published a preliminary note on some incomplete observations made in his laboratory, according to which an agglutination of platelets occurs in anaphylactic shock. He was inclined to attribute a central importance to the phenomenon, ascribing the symptoms of the anaphylactic shock to cerebral capillary embolisms produced by these clumps of platelets.

4. *Relation of the blood changes to the shock.* The changes in the corpuscular content of the blood are sufficiently striking to raise the question whether they afford an adequate explanation of the phenomena of the shock, or of any part of these phenomena. We have seen that the rapid increase in the proportion of red corpuscles is entirely accounted for by the loss of plasma from the blood vessels. This loss, as calculated from the change in hæmoglobin value or relative corpuscular volume, is frequently of such dimensions that the mere reduction of the volume of

the blood must have a serious effect on the efficiency of the circulation. For example, in one experiment quoted the relative corpuscular volume rose from 30 to 50 p.c. Assuming that the volume of the corpuscles remains stationary, this means a loss of four-sevenths of the plasma. The cat weighed 2·6 kilo., and may be taken to have had about 160 c.c. of blood. Of this 70 p.c. or 112 c.c. would originally be plasma, and 48 c.c. corpuscles. During the shock the volume of the plasma became equal to that of the corpuscles, *i.e.* 48 c.c., so that 64 c.c. had left the circulation. The volume of the circulating fluid, in other words, underwent a reduction of 40 p.c. Now such a reduction of volume, produced by simple hæmorrhage, causes a fall of the blood-pressure to a low level; according to Bayliss spontaneous recovery of the blood-pressure to its initial level does not occur in a decerebrated or anæsthetised cat after bleeding to this extent. On the other hand, the type of circulatory depression produced by such a hæmorrhage is not that produced by histamine; there is not in the former case the extreme reduction of cardiac output and accumulation of the remaining blood at the periphery which histamine produces. It must be remembered, however, that after hæmorrhage in the normal animal fluid is abstracted from the tissues and passes into the blood, so that the volume of the circulating fluid is at least partially restored, and its viscosity diminished. In histamine shock such a restorative mechanism cannot come into play; the loss of volume is due to the opposite process of passage of fluid from the blood into the tissues.

It might well be urged, moreover, that in histamine shock the effect of reduced volume is complicated by that of increased viscosity of the blood, caused by the rise in the proportion of red corpuscles and possibly by obstruction to flow through the capillaries by aggregation of platelets. Thickening of the blood by increase of corpuscular content, and increase of peripheral resistance by partial blockage of capillaries, would not by themselves cause collapse of the arterial pressure. The increase of the peripheral resistance from both causes would, on the contrary, cause the arterial pressure to rise if the output from the heart were maintained. It could not, however, be assumed that it would produce the same effect when associated with a serious reduction of the blood volume. It might be argued that the lowering of the cardiac output would so reduce the arterial pressure that it would be inadequate to drive the thickened blood through the peripheral resistance, so that blood would tend to accumulate in the capillaries, the return of blood to the heart would become deficient, and the output would further decline.

It is very probable that a vicious circle of this type does, indeed, play some part in the production of histamine shock, as seen in many of our experiments. It is easy, however, to show that this combination of lowered volume and increased viscosity is not the only factor in the production of the condition, or even the most important one. A consideration of the figures in Table II will make it clear that there is no close correspondence between the degree of concentration and the severity of the circulatory depression. The lack of correspondence, however, is even greater than the figures in this table suggest. It is possible to produce a condition of severe shock by injection of histamine, without any material change in the relative volumes of red corpuscles and plasma in the general circulation; on the other hand, cases have occurred in our experience, though rarely, in which, while the blood changes were pronounced, the animal escaped such impairment of the circulation as could be held to constitute "shock."

We may consider first the occurrence of shock without significant concentration. Cases of this kind have occurred even when the histamine was injected rapidly, in a single large dose, but these have been exceptional. On the other hand when histamine is given by slow infusion, so that its entry into the circulation is spread over 20 to 30 minutes, absence of serious concentration is the rule, though the shock may be pronounced. One experiment illustrating this point has already been quoted, but it will be of interest to give here the details of another, in which measurements of blood volume were carried out. Such measurements bring to light the very significant fact that, even when the corpuscular content gives no evidence of loss of plasma in the histamine shock, the volume of blood in effective circulation is nevertheless reduced.

Cat weighing 2·5 kilo. Ether anæsthesia. Record of carotid blood-pressure. Blood samples from the other carotid.

3.53 p.m. B.P. 224 mm.—took 6 c.c. of blood. Hæmoglobin 88 p.c. Hæmatocrit 38 p.c.
3.58 ,, Inject 1 c.c. vital red (1 p.c.) by femoral vein.
4.1 ,, B.P. 156 mm. Bled 6 c.c. for colorimetric determination. Hæmatocrit 37·5 p.c. Plasma volume (by colorimeter) 100 c.c. Blood volume 160 c.c. Animal left (under ether) till 4.55 p.m.
4.55 ,, B.P. 144 mm. (steady). Hæmoglobin 80 p.c. Hæmatocrit 35 p.c.
4.57 ,, Began to run in 0·05 p.c. histamine solution very slowly. Blood-pressure fell rapidly.
5.4½ ,, 2 c.c. (=1 mgm.) infused. B.P. 62 mm. Respiration fails. Artificial respiration on.
5.14 ,, 4 c.c. (=2 mgm.) infused. B.P. 64 mm.
5.26 ,, 8 c.c. (=4 mgm.) infused. B.P. 62 mm. Output of heart very small. Stop infusion. Irregular convulsive inspirations.

5.27 p.m. Took 6 c.c. of blood. B.P. falls to 45 mm. Output hardly perceptible on manometer. Hæmoglobin 90 p.c. Hæmatocrit 39·5 p.c.

5.28 „ 1 c c. of vital red (1 p.c.) by femoral vein.

5.31 „ Bled 6 c.c. for colorimeter. B.P. falls to 32 mm. Irregular inspiratory gasps continue during artificial respiration. Output of heart almost imperceptible.

Plasma volume (colorimeter) = 73 c.c. Hæmoglobin = 90 p.c. Blood volume = 120 c.c.

There are several points in this record deserving careful attention. The shock produced by the method of slow infusion is less severe than that which usually follows a similar dose given rapidly. The addition of a small hæmorrhage, however, intensifies the effect, so that the circulatory failure is ultimately as complete as that produced by sudden injection. Clearly the animal is suffering from defective volume of circulation. This, however, is not at all suggested by the readings of the hæmatocrit or hæmoglobinometer. The final concentration is represented by a hæmatocrit reading of 39·5 p.c. only, as compared with 38 p.c. originally and 35 p.c. after bleeding to the extent of 12 c.c. What proportion of the loss indicated by the colorimeter is due to the loss of plasma which such a small change indicates? The calculation, which is somewhat complicated by the bleedings, may be most simply made as follows.

The reading at 4.55 p.m. shows that the volume lost by the bleeding made for the colorimeter at 4.1 has been made good by the normal dilution of the plasma. The volumes at 4.1 were blood 160 c.c., plasma 100 c.c., corpuscles 60 c.c. 6 c.c. were taken of which $6 \times \frac{6}{16}$ c.c. = 2·25 c.c. were corpuscles. At 4.55, then, we have 57·75 c.c. of corpuscles and 102·25 c.c. of plasma, giving still 160 c.c. of blood, and a hæmatocrit reading of 35 p.c. This rises after histamine to 39·5 p.c., so that the calculated plasma has fallen to $57{\cdot}75 \times \frac{60{\cdot}5}{39{\cdot}5} = 88{\cdot}5$ c.c., and the blood volume to 88·5 + 57·75 c.c. = 146·25 c.c. We remove 6 c.c. of blood at 5.27, before the sample taken for the colorimeter, without further disturbance of the proportion of corpuscles, so that this volume may be simply subtracted, giving us, at the time of the bleeding for the colorimeter, a volume of just over 140 c.c., as estimated from the loss by concentration and bleeding. The determination by vital red, however, shows a volume of only 120 c.c.—*i.e.* it indicates a loss in effective blood volume of 40 c.c., of which only 20 c.c., just one-half, are accounted for by bleeding and by the loss of plasma indicated by the concentration.

It is clear that such a discrepancy must mean either that the vital red does not determine the whole blood volume in these circumstances, or that the hæmatocrit does not give a true indication of the average corpuscular content of the blood in the body. Possibly both sources of

error are present. Both would ultimately depend on the stagnation of part of the blood at the periphery. The vital red method determines the volume, the hæmatocrit the corpuscular content, only of the blood which is in effective circulation.

The converse condition, of pronounced concentration of the blood associated with but slight symptoms of shock, has occurred also in our series of experiments. In the following experiment a striking and rapid increase of corpuscular content was associated with only a slight depression of the circulation.

Cat weighing 2·1 kilo. Chloroform, then ether. Cannulæ for record and injection as usual. Vagi cut.

5 p.m. B.P. 160 mm. Blood sample 1 for estimation. Hb. = 74 p.c.

5.6 „ 3 mgm. of histamine intravenously. Small preliminary fall of B.P., then prolonged recovery to about 165 mm. with subsequent slow decline to 120 mm. Manometer pulse reduced, but still such as to show good output.

5.11 „ 4 mgm. of histamine intravenously. Blood-pressure rises briefly to 130 mm. and then sinks slowly to 100 mm. Respiration fails. Artificial respiration applied. Output now obviously reduced, but not very small.

5.17 „ Blood-pressure begins to rise slowly and attempts at natural respiration appear.

5.18 „ Blood sample 2 for estimation. Hb. = 106 p.c.

5.20 „ Spontaneous respiration. Abdomen opened. Bowels congested and somewhat cyanosed. Network of venules clearly visible. Small veins show beaded constriction. Arterioles reduced to small threads. Pancreas dusky in colour, with gelatinous œdema.

The hæmoglobin values indicated the passage of much plasma from the vessels; if the original corpuscular content was 33 p.c. the change represents a loss of about 40 p.c. of the plasma. There was a distinct, though not very pronounced, leucopenia of the usual type, and the customary presence of clumps of platelets in films taken during the action of histamine. The changes in the cellular constituents of the blood and the calculated loss of plasma were, therefore, as great as those seen in most cases of severe shock, and greater than in many. Nevertheless the arterial pressure never fell below 100 mm., the output from the heart, though reduced, never fell to a shock-like minuteness, and both blood-pressure and heart output soon began to recover from even this small degree of depression.

It seems safe to draw the conclusion that the leakage of plasma from the vessels into the tissues, with the reduction in the volume and increase in the viscosity of the blood which it entails, cannot be the main cause of the shock, though it doubtless accentuates its severity. The characteristic features of the condition are due not so much to the fact that the volume of the blood is reduced, as to the tendency of what remains to

stagnate at the periphery in the capillaries and venules instead of returning to the heart.

5. *The cause of the peripheral accumulation of the blood.* When we had arrived at the conclusion just stated, it appeared to us that the only type of effect, which could account for the phenomenon we were attempting to analyse, was a relaxation of the tone of the capillary blood vessels. No direct evidence was then available, which would warrant the assumption that histamine could produce an effect of this kind. It has since been provided, however, by the results, already published, of an investigation in which one of us cooperated with A. N. Richards(3). These experiments led to the conclusion that the paradoxical vasodilator action of small doses of histamine, which our earlier work had left unexplained, is due to a direct depression of the normal tone of the capillaries, the plain muscle of the arterioles being always stimulated to increased tone by doses of histamine large enough to affect it at all. Evidence was obtained, in the same series of experiments, in support of the view that other vasodilator substances, of which acetyl-choline was a type, produce their effects entirely on the muscular coats of the arterioles, though the records obtained of their action, with manometer and plethysmograph, showed a remarkable superficial resemblance to similar records of the action of small doses of histamine. According to our view, however, of the nature of the histamine shock, an intensification and prolongation of the action of an arterial dilator, such as acetyl-choline, should produce an effect of an entirely different kind; in particular the accumulation of blood at the periphery, characteristic of the action of large doses of histamine, should not be produced by a vasodilatation limited to the arteries.

We chose acetyl-choline for these experiments, rather than the nitrites, since the latter group cannot be used for producing the prolonged and intense effect which we required, without introducing complications due to their action on the hæmoglobin of the corpuscles. With acetyl-choline a large single dose is unsuitable. As has been shown by Hunt(10) and by Dale(11), with any but minute doses of this substance an intense vagus-like inhibition of the heart is superimposed on the vasodilator effect. Its action, however, is so evanescent, owing to its rapid hydrolysis in the body, that we found it possible, by a carefully adjusted very slow infusion of a dilute solution (0·01 p.c.) into the vein of a cat under ether, to produce a persistent low blood-pressure for upwards of 30 minutes by vasodilatation alone, without causing inhibition of the heart. We have performed the experiment a number of

times, with uniform result. The arterial pressure fell rapidly with the commencement of the infusion, and could be kept steady at a level of 40–50 mm. by controlling the rate of inflow, which usually had to be very slightly accelerated as the experiment proceeded. The heart beat rapidly, and usually showed some irregularity of rhythm, but the output remained thoroughly efficient, as judged by the excursions of the manometer and by the general state of the circulation. The intestines showed a pink flush and pulsated obviously, and the great veins were well filled, but not over-distended. Samples of blood taken before the infusion and during its progress showed that a slow dilution of the plasma was taking place. Spontaneous respiration sometimes continued throughout the experiment, but periods of artificial respiration were necessary in some cases. Perhaps the most striking contrast with the effect on the circulation produced by histamine, when similarly administered, was presented by the events following the stoppage of the infusion. After acetyl-choline the arterial pressure began immediately to rise from the low level at which it had been maintained, and with an extraordinary rapidity regained or surpassed the level at which it had stood before the infusion began. After similar treatment with histamine the typical picture is the shock which we have described in detail above. Usually there is in this case no sign of spontaneous recovery; the arterial pressure can be driven up and the output of the heart temporarily restored by compression of the limbs and abdominal vessels, only to fall away with relaxation of the compression, as the blood slowly accumulates again at the periphery, and the heart and great vessels are again depleted.

In favour of our view that the shock-like failure of the circulation is due to accumulation of the blood in relaxed capillaries we have, then, the positive evidence that histamine has been shown to relax capillaries, and the negative evidence that acetyl-choline, which appears to dilate the arterioles only, does not produce a condition in any way resembling shock.

There is one point, however, which needs further explanation. The effect of small doses of histamine, which Dale and Richards attributed to relaxation of capillary tone, presents the typical features of a vaso-dilator action; during the fall of arterial pressure caused by such small doses the output of the heart is increased, as we showed in our first paper on the action (1). The action, in other words, is due to weakening of the peripheral resistance, and is not a volume effect diminishing the return to the heart. In effect, therefore, though not in location, the action of these small doses is practically identical with that of the arterial

dilators. Why should the two types of action have outcomes so widely different when both are intensified and rendered persistent?

We believe that the answer to this question is to be found by considering the normal state of the flow of blood through the capillaries. All who have studied it under the microscope have been struck by the comparatively small part of the available capillary network used for conveying the blood under normal conditions. Langley (12) has pointed out how under conditions of low pressure the path of the blood may be changed by the closing down of the capillaries in one area and the opening up of those in another. It may be supposed that, though distribution is constantly changing, the total capillary path available at any moment normally varies but little. A small dose of histamine, the effect of which will spread hardly beyond those capillaries which provide a path for the blood during the brief period of its action, will produce simply an evanescent widening of that path, of which the effect will differ but little from that of an evanescent arterial relaxation. When the effect is intensified or rendered more persistent by large dosage, we suppose that a different set of factors comes into play. Not only the tone of the capillaries in actual use when the effect begins, but that of the whole network potentially available now comes under the action of the drug. With a simultaneous loss of tone of the capillaries throughout the body their capacity for holding blood rises far beyond the normal average, and the blood spreads and percolates into the whole network of patent channels as into a sponge, so that the outflow into the veins and back to the heart at once begins to fail. Constriction of the arterioles will mitigate the increase in the total capacity of the system caused by relaxation of the capillaries, and by maintaining a high peripheral resistance will hold up the arterial pressure, which will only fall gradually as the output from the heart decreases. But though arterial constriction delays the fall of pressure in the arteries, it cuts off that pressure the more effectively from the blood in the capillaries, and with the wane of the output from the heart the flow through the capillaries becomes ever slower and the tendency to stagnation greater, till ultimately only a relatively small part of the available blood is effectively circulating. A relaxation of arterial tone at this stage, whether from the passing of the vaso-constrictor effect of histamine or failure of the anæmic vasomotor centre, will further increase the capacity of a system, for the filling of which the blood is already inadequate.

The true significance of the loss of blood volume owing to escape of plasma can now be appreciated. It may be noted, in the first place, that

it is probably another aspect of the same poisonous action of histamine on capillary endothelium. We may suppose that an intensification of the action which relaxes the normal capillary tone renders the endothelium abnormally permeable, so that it no longer retains the plasma. It is readily intelligible, therefore, that the loss of plasma from the blood should be a more conspicuous feature of the effect as produced by sudden introduction of a large dose of histamine than of that produced by slow infusion. It will be observed also that this association of increased vascular capacity and low blood-pressure, with diminution of volume and concentration of the blood, involves the abrogation of one of the normal compensatory processes of the body. Low blood-pressure, as produced by relaxation of arterial tone, is accompanied by a passage of water from the tissues into the blood, reducing the disparity between the volume of the blood and the capacity of the system. If the corpuscular content is estimated in small samples of blood, taken during the fall and recovery of arterial pressure which follow a small dose of amyl nitrite, for example, it is found that the curve of dilution and reconcentration follows that of the arterial pressure with great accuracy. With the fall produced by histamine this compensatory process of dilution is not merely absent, but reversed; the effect of increased capacity is accentuated by decline of blood volume.

While we are convinced that general dilatation of the capillaries and loss of plasma from the blood are main factors in the production of the shock, we are not in a position to exclude others. The stagnation of blood in the capillaries which occurs in inflammation has been thought by some observers to be the result of a change in the endothelium of such a nature as to hinder the flow of blood through the small channel, though no clear conception has been put forward as to what the nature of such a change could be. There are theoretical difficulties in the way of supposing that a mere change in the physical properties of the surface of the endothelial cells could produce such an effect, and Trevan(13) has recently maintained that the stasis is sufficiently explained by local concentration of the blood and consequent increase in its viscosity. We have been unable to put these possibilities to the test of experiment, so that it is sufficient to admit that, if other changes than those which are clearly recognisable play a part in the stasis of inflammation, they are possibly concerned also in the peripheral stasis produced by histamine. It must be recognised that there is no general agreement as to the factors determining the rate of flow through the capillaries. The conditions which we have called "relaxation" and "tone" of capillary walls do not

necessarily correspond with the phenomena so called in the case of plain muscle. They may simply represent the effects of imbibition and loss of water by the endothelial cells. Leonard Hill(14) maintains that "the influence on the capillary circulation of osmotic and surface energy can be no less than that effected by the heart and vasomotor system," and points out that "in the active conditions of life the contents of the capillaries are continually being emptied onwards by the contractions of the skeletal muscles, pressure against external bodies and the influence of gravity in changes of posture." As regards surface energy the suggestion is not yet sufficiently definite to enable us to consider whether changes of this kind play any part in the action of histamine; but it can hardly be doubted that the loss of tone and movement of the voluntary muscles will accentuate the tendency to peripheral stagnation when the shock is fully developed. Occasionally an animal in this condition performs a movement of the nature of a convulsive inspiration or a vomiting effort, and the accelerated return of blood to the heart is at once obvious in a temporary rise of arterial pressure and increase of output.

We may summarise our conclusions, as to the cause of the peripheral accumulation of blood after a large dose of histamine, by saying that we regard it as principally the effect of a general relaxation of the capillary vessels; that the loss of blood volume owing to morbid permeability of the endothelium accentuates the effect of this relaxation in producing a relative deficiency of blood volume in proportion to the capacity of the system; that the lack of the normal favouring influence on capillary flow exerted by movement of the voluntary muscles probably plays some part; and that, in addition to the widening of the capillary channels and the thickening of the blood by loss of plasma, there may be other factors favouring stasis in the capillaries which only further investigation can define.

Some Practical Applications and Analogies.

It will hardly have escaped notice that the conception of the action of histamine, to which our analysis has led us, embodies the main features of a reaction which, if it occurred locally, would be recognised as a mild inflammation. The widening of capillary lumina, the opening up of channels normally empty, the transudation of plasma through abnormally permeable endothelium and the tendency to stasis of the concentrated blood—these phenomena, when occurring in an area so restricted that the general arterial pressure is not materially affected, will produce the familiar sequence of redness, swelling and œdema. This, indeed, is the

effect of histamine when locally applied, as Sollmann and Pilcher(23) have shown; applied even in high dilutions to the lightly scarified human skin histamine causes redness, swelling and the formation of an œdematous wheal.

In its general action on the other hand, when introduced into the circulation in large doses, histamine reproduces in a very suggestive manner the complex which in recent years has come to be recognised as characteristic of one kind of traumatic shock. The collapse of arterial pressure in spite of arterial constriction, the weakening of the pulse out of proportion to the fall of arterial pressure, the rise in corpuscular content of the blood owing to loss of plasma, the fall in cardiac output, in spite of but slight impairment of the activity of the heart, owing to a fall in effective blood volume in excess of that due to loss of plasma—all these phenomena, as well as the associated depression of the respiratory centre, fall of body temperature and general lethargy, can be found in the descriptions of surgical or traumatic shock by Malcolm(15), Y. Henderson(16), Mann(17) and others. The concentration of the blood by loss of plasma had been earlier recognised by Sherrington and Copeman(24) as a characteristic feature of shock. Some years ago we drew attention to the many points of similarity between the action of histamine and the so-called "anaphylactic shock." The resemblance to some cases of shock following trauma seems to be even closer than to the anaphylactic reaction, which has been called "shock" by analogy.

The parallel becomes even more suggestive when it is remembered that local trauma, when not so severe that its effect is complicated and obscured by effusion of blood from ruptured vessels—for example, a blow on the skin from a cane or a whip—will cause the same sequence of capillary flushing and wheal-formation as the dermal application of histamine. So that we have locally applied histamine reproducing the effect of a mild local injury of the tissues, and histamine distributed through the system reproducing the sequel to a massive injury of tissues.

The action of histamine does not stand by itself, but represents in its most characteristic features a type of action common to a large group of poisonous substances of animal or bacterial origin. Substances having this type of action have been extracted from most of the organs of the body, though it is unlikely that histamine itself is among them, except in special cases such as that of the intestinal mucosa. (Barger and Dale(18).) It may be noted, however, that other substances of this class —*e.g.* bee poison or certain bacterial products—can produce either local

inflammation and œdema or profound circulatory collapse, according to the method of application and the magnitude of dosage. A poisoning of the capillary endothelium seems to be the common factor in the action of all. This again brings them into relation with certain metallic poisons, such as arsenic and gold salts, which were long ago classed by Heubner(19) as "capillary poisons," and which, when introduced in appropriate doses into the general circulation, produce a shock-like prostration. The shock-like symptoms which have occasionally followed the intravenous administration of salvarsan probably depend on an effect of this type--an acute endothelial intoxication.

The existence of these points of community, in the action of substances so utterly unrelated chemically as histamine and certain metallic ions, forbids any assumption that the production of similar effects, by unknown constituents of some organ or tissue, indicates the presence therein of histamine itself, or of any substance chemically related to it. The similarity depends on the fact that all act on the endothelium, and produce in it changes probably of the same general type. A hint, as to what the nature of these changes may be, is possibly provided by the fact that the anaphylactic reaction, more especially in those species in which histamine exhibits this type of action, also presents the picture of an acute endothelial poisoning. All available evidence goes to show that the anaphylactic antibody is of the nature of a "precipitin," the interaction of which with the corresponding antigen results in a change in the state of dispersion of the colloidal particles. One of us (Dale(25)) has given reason for believing that the occurrence of this reaction actually in the plain muscle fibres of the guinea-pig is the exciting cause of the contraction of the plain muscle, which gives to the anaphylactic "shock" its characteristic type in that species. It is not inconceivable that a physical change of this type occurring in the endothelial cells would lead to relaxation of their tone and ultimately to abnormal permeability; indeed if the anaphylactic reaction, as exhibited in different tissues and species, depends always on the same type of interaction between antigen and antibody, this would almost of necessity follow. So that it is quite possible that the production by histamine, and by a whole group of other substances, of a complex including contraction of plain muscle with relaxation and permeability of capillaries, may depend on a common type of physical change in protoplasm produced by all of them, the result of which receives different expression in terms of the physiology of different tissues. At this point, however, speculation without further basis of fact becomes fruitless.

A new and practical importance has been given to this type of action by recent work of Bayliss(20) and of Cannon(21). We have pointed out above how the local effects of injury may resemble those of histamine. Bayliss and Cannon have provided a rational basis for the similarity, mentioned above, between the shock produced by histamine and that following trauma, by direct evidence that shock follows extensive injury to the tissues of a limb, the nervous connexion of which with the rest of the body has been severed, but that it is prevented by clamping the blood vessels. They conclude that an important role in the genesis of shock is played by absorption into the general circulation of products liberated by the injury of tissues—their experiments deal especially with skeletal muscle—having the type of action which we have been discussing. Delbet and Quénu(22) have independently developed similar views of the importance of a chemical factor in shock. The presence of large quantities of substances having this action in the contents of the stomach and intestine is suggestive in connexion with the pronounced association of shock with injuries of those viscera, and on the ease with which rough handling or excessive exposure of them determines its onset. Whatever may be the ultimate conclusion as to the importance of such factors in surgical shock, the recognition of this traumatic toxæmia provides an important addition to the points of community in causation, which are gradually coming to light, between a number of physiological and pathological phenomena, the symptomatic similarity of which has long been recognised.

Summary.

In doses of the order of 1 mg. per kilogram and upwards histamine produces in the anæsthetised cat a condition presenting numerous points of resemblance to traumatic and surgical shock. The central feature of the condition is an oligæmia, partly due to passage of plasma out of the blood vessels, partly to retardation of the flow of blood at the periphery. Evidence is given in favour of the view that this is due to a general loss of tone by the capillaries throughout the body. The excessive permeability of these vessels, which allows escape of plasma, is regarded as a further stage of the same type of action. This type of effect appears in the action of a large number of substances, some of them having no kind of chemical relationship with histamine. The nature of the common factor in the effect of these, and its relation to the similar symptoms seen in the anaphylactic reaction, in shock, etc., are discussed.

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